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Perspectives in Pharmacology

Intrinsic versus Idiosyncratic Drug-Induced Hepatotoxicity—Two Villains or One?

Robert A. Roth and Patricia E. Ganey

Department of Pharmacology and Toxicology, Center for Integrative Toxicology, Michigan State University, East Lansing, Michigan

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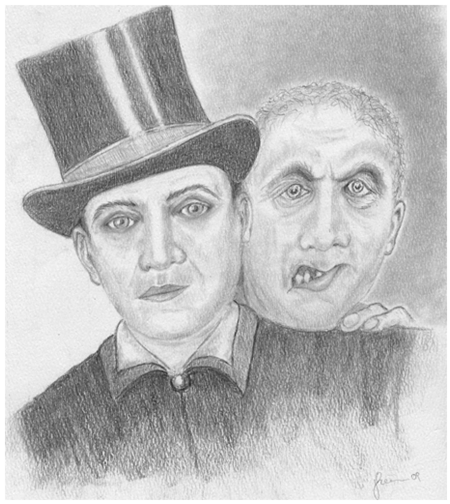
ABSTRACT

"Intrinsic" and "idiosyncratic" drug-induced liver injury reactions are commonly thought to arise by different modes of action. Intrinsic toxicity is reproducible in animals and occurs dose-dependently at sublethal doses. Environmental and genetic sensitivity factors can influence the toxicity of intrinsic hepatotoxicants. Among these is inflammatory stress. For example, exposure of mice to inflammatory bacterial lipopolysaccharide (LPS) causes a leftward shift in the dose-response relationship for acetaminophen hepatotoxicity; that is, acetaminophen toxicity is enhanced by LPS-induced inflammatory stress. Idiosyncratic reactions present themselves very differently than intrinsic ones; they happen in a minority of patients, with variable time of onset and no obvious relationship to drug dose, and they are not reproducible in usual animal tests. Although these characteristics seem to distinguish them from intrinsic reactions, consideration of fundamental principles of dose response can explain the differences. For a drug that causes idiosyncratic hepatotoxicity, the liver may not be a typical target for toxicity because the dose-response curve for hepatotoxicity lies to the right of the lethal dose. However, a sporadically occurring sensitivity factor, such as an inflammatory episode, could shift the dose-response curve for hepatotoxicity to the left, thereby bringing hepatotoxic doses into the therapeutic range. This hypothesis can account for the bizarre characteristics of idiosyncratic reactions and is supported by recent results showing that several drugs associated with human idiosyncratic reactions can be rendered hepatotoxic to rodents upon interaction with an inflammatory stimulus. In light of this view, intrinsic and idiosyncratic reactions may not be that different after all.

Once upon a time, there were two toxicities, "intrinsic" and "idiosyncratic," recognized widely to be very different villains. Although both are unsavory characters, intrinsic toxicity behaves predictably, and for the most part, his presence can be avoided with appropriate precaution. He is gentlemanly, obeying the dictates of classic toxicologic protocol by acting in a dose-dependent manner and with remarkable consistency within and across species (Table 1). When the great-great-great grandfather of toxicology, Paracelsus, declared that "all things are toxic, it is only the dose that distinguishes a remedy from a poison," he was, of course, referring to this intrinsic toxicity fellow.

Idiosyncratic toxicity is the more diabolical of the two characters. Enveloped in a dark cloak that hides his menacing countenance, he seems to sneer at the laws of dose response. Even when illuminated under the lamppost of conventional



wisdom, he remains all but invisible to the eyes of preclinical safety testing. This menace lurks in the shadows of drug efficacy, pouncing unpredictably to attack unsuspecting vic-

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ABBREVIATIONS: APAP, acetaminophen; LPS, lipopolysaccharide; NSAID, nonsteroidal anti-inflammatory drug; IADR, idiosyncratic adverse drug reaction.

TABLE 1
Two hepatotoxic villians

Intrinsic	Idiosyncratic
Affects all individuals at some dose	Attacks only susceptible individuals
Clearly dose-related	Obscure relation to dose
Predictable latent period after exposure	Variable onset relative to exposure
Distinctive liver lesion	Variable liver pathology
Predictable using routine animal testing	Not predictable using routine animal tests

tims (Table 1). The balance of this tale focuses on these two villains: are they two individuals, like Count Dracula and the Frankenstein monster, or one individual with two faces, like Dr. Jekyll and Mr. Hyde?

Intrinsic Hepatotoxicity

Toxicologists often refer to a "target organ" as a site in the body at which damage occurs (Lehman-McKeeman, 2008). The liver is a target for many intrinsically toxic xenobiotic agents, including many drugs. A minimal requirement for designation as a target organ is that injury to the tissue must occur at doses below those that are lethal. Thus, the liver is depicted as the target organ in Fig. 1. As noted above, this type of toxicity is dose-related; that is, as exposure increases, a threshold is reached, above which individuals respond with toxicity that becomes more severe with increasing exposure (i.e., dose).

Drug-induced liver injury is the leading cause of death from acute liver failure in the United States and the most frequent reason for withdrawal of drugs from the market (Bleibel et al., 2007; Senior, 2007). Acetaminophen (APAP) targets the liver, and overdose from this drug alone is responsible for approximately half of cases of acute liver failure in the United States (Bleibel et al., 2007; Gunawan and Kaplowitz, 2007). It causes dose-related hepatotoxicity in humans and animals and, because of the clinical importance of its toxicity, has become the most studied of agents that cause intrinsic hepatotoxicity. As with many other hepatotoxic xenobiotic agents, metabolic bioactivation of APAP is the initiating event in the pathogenesis. This leads to covalent binding of reactive metabolite to cellular constituents and the triggering of secondary mechanisms that allow initial stress to the liver to progress to hepatocellular necrosis. These progression factors and events are numerous and may depend on dose or other exposure conditions as well as environmental and genetic factors. They include activation of several nonparenchymal cell types (Kupffer cells, natural killer/natural killer T cells, endothelial cells, etc.) and intracellular signaling pathways, disruption of mitochondria, production of cytokines and reactive oxygen and nitrogen species, hemostasis, interference with replicative repair, and so on (Fig. 2) (Ganey et al., 2004, 2007; Gunawan and Kaplowitz, 2007).

Inflammatory Stress as a Determinant of Sensitivity to Intrinsic Hepatotoxicants

It is well known that people vary rather markedly in their sensitivity to the toxic effects of drugs and other chemicals. For example, large variations in susceptibility to APAP hepatotoxicity exist in humans and animals. Some people who consume APAP respond with increases in markers of liver injury at daily doses (4 g/day) in the therapeutic range, whereas most people are much less sensitive (Watkins et al., 2006).

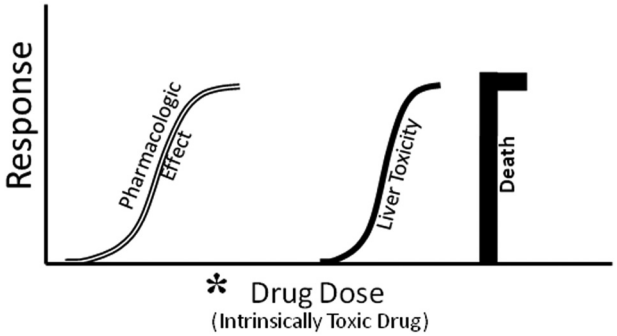

Fig. 1. Intrinsic toxicity. To be a useful drug, pharmacologically effective doses must lie to the left of those that cause toxicity and death. The asterisk represents a therapeutically useful dose that is nontoxic. As dose of a drug or other toxicant increases, a threshold is reached, above which injury occurs to one or more organs. The severity of injury is dose-related, and tissues vary in their sensitivity to toxicants. Here, the liver is represented as a "target organ," inasmuch as it responds with injury at doses smaller than those that cause death or injury to less sensitive organs.

One environmental determinant of susceptibility appears to be inflammatory stress. The inflammatory response often begins with exposure to microbes or their products. Of these, lipopolysaccharide (LPS) from Gram-negative bacteria has received the most attention. Microbial products activate a variety of cells by binding to Toll-like receptors and initiating intracellular signaling pathways that culminate in the production and/or release of numerous mediators of inflammation. These mediators include several transcription factors, bioactive lipids such as prostanoids and leukotrienes, various cytokines and enzymes, reactive oxygen and nitrogen species, and so on (Fig. 3). Through the actions of these factors, other cells become activated and tissue homeostasis is altered. The response usually culminates in the elimination of pathogenic microbes from tissues and thus is typically beneficial. However, if too pronounced, it can injure organs of the host. Indeed, inflammation can be viewed as a collage of stresses that must be tightly controlled to avoid damage to tissue.

It is easy to understand that a tissue homeostatically altered by inflammatory stress could be hypersensitive to a secondary stress imposed by exposure to a toxic xenobiotic agent. For example, a comparison of the factors and events involved both in the progression of APAP hepatotoxicity (Fig. 2) and in the inflammatory response (Fig. 3) reveals much in common and hence the potential for interaction that could enhance injury. Indeed, APAP consumption interacts in humans with hepatitis viruses (i.e., inflammagens that target the liver) to increase the risk for serious liver injury (Yaghi et al., 2006: Moling et al., 2006; Kc, 2007; Nguyen et al., 2008). Likewise, we reported recently that infection of mice with a virus that induced hepatic inflammation rendered nontoxic doses of APAP hepatotoxic (Maddox et al., 2010).

Another susceptibility factor in human APAP-induced liver failure is alcohol consumption. The ability of alcohol to depress mitochondrial glutathione and enhance bioactivation of APAP is widely held to underlie the hepatotoxic APAP-alcohol interaction (Slattery et al., 1996; Tanaka et al., 2000; Zhao and Slattery, 2002); however, ethanol also increases

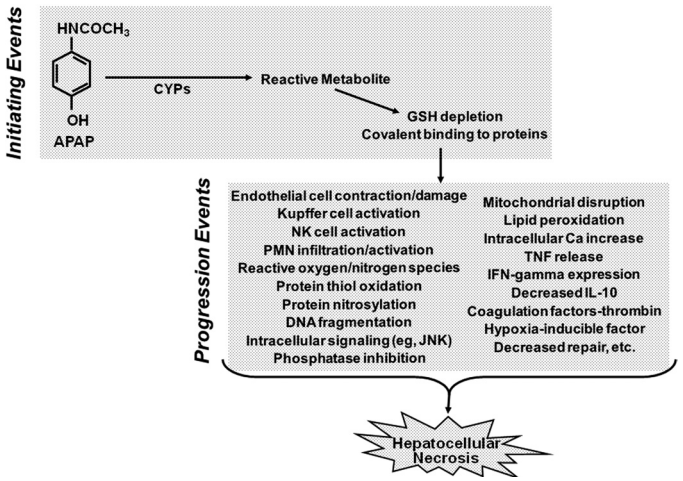

Fig. 2. Initiation and progression events in acetaminophen (APAP) hepatotoxicity.

systemic exposure to LPS, presumably by increasing intestinal permeability to this inflammagen (Bode and Bode, 2003, 2005; Purohit et al., 2008). It is noteworthy that mice treated with a modestly inflammatory dose of LPS became more sensitive to APAP-induced liver injury; that is, LPS coexposure caused a leftward shift in the dose-response curve for APAP hepatotoxicity, causing normally nontoxic doses of APAP to become hepatotoxic (Maddox et al., 2010). Thus, the ability of ethanol to enhance intestinal translocation of LPS to the liver is likely to play a role in its hepatotoxic interaction with APAP.

Research over the past decade or so has revealed that LPS interacts with numerous intrinsically hepatotoxic agents. These include carbon tetrachloride, monocrotaline, cocaine, aflatoxin B1, and others (reviewed in Ganey et al., 2004). The results support the idea that inflammatory stress can sensitize the liver to injury from a variety of intrinsic hepatotoxicants (Fig. 4A).

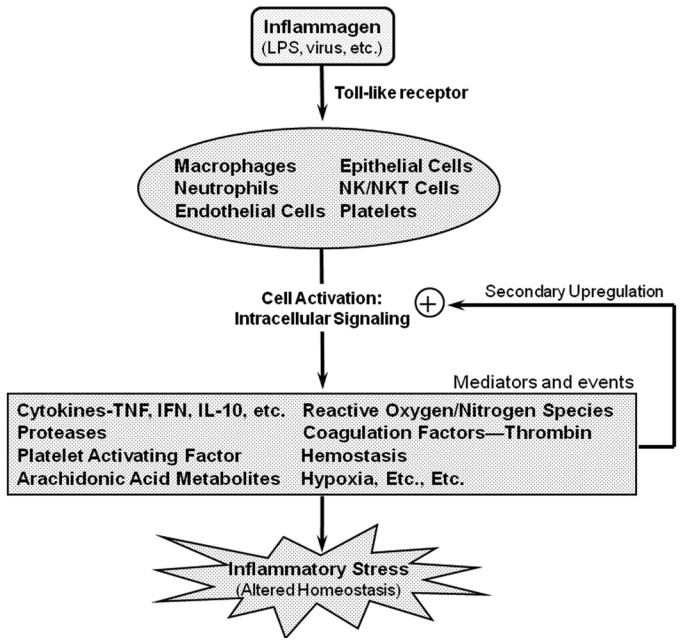

Fig. 3. Simplified view of the inflammatory response. Inflammation is often initiated by agonists such as LPS that bind to Toll-like receptors on various inflammatory cells. In the liver, this activates Kupffer cells and sinusoidal endothelial cells, resulting in release of numerous inflammatory mediators. Some of these mediators can feed back to enhance these responses and activate other cells. The resulting "inflammatory stress" entails an alteration in tissue homeostasis that can either be beneficial (e.g., microbial killing), harmful (e.g., septic shock, multiple organ injury), or harmless depending on its magnitude.

Idiosyncratic Hepatotoxicity and Inflammatory Stress

In recent years, drug candidates that cause intrinsic liver injury are usually weeded out in preclinical testing, so that much of the drug-induced liver injury that occurs from recently marketed drugs is idiosyncratic. Idiosyncratic hepatotoxicity is most often not related to a drug's pharmacological action. For example, trovafloxacin has caused serious hepatotoxicity in patients, whereas levofloxacin, an antibiotic in the same fluoroquinolone class, is without this liability. On the other hand, nonsteroidal anti-inflammatory drugs (NSAIDs) that are nonspecific inhibitors of cyclooxygenases 1 and 2 (e.g., diclofenac, sulindac) all seem to have the capacity to cause liver injury in people, so that the potential to cause idiosyncratic hepatotoxicity seems to apply to this entire class of drugs.

The list of drugs that cause idiosyncratic hepatotoxicity is long and continues to grow in part because no effective preclinical tests have emerged that can identify drug candidates

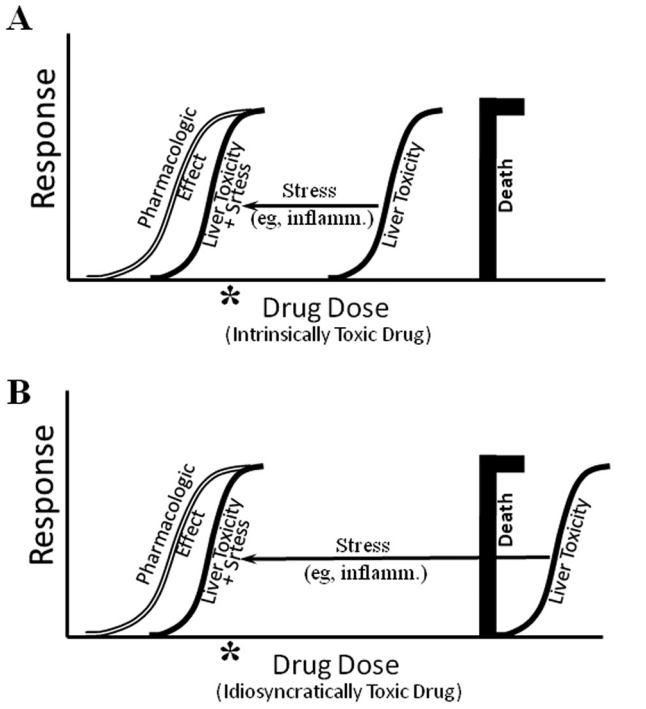

Fig. 4. Susceptibility to intrinsic (A) and idiosyncratic (B) hepatotoxicities: a dose-response perspective. For drugs that cause intrinsic hepatotoxicity (e.g., APAP), substantial differences in individual sensitivity can occur. One way in which such differences arise is through stresses such as inflammation that can change one's sensitivity to the toxic effects of the drug. This manifests as a leftward shift in the dose-response curve for hepatotoxicity (A). Drugs that cause idiosyncratic toxicity do not cause liver injury in most patients. This may be because the dose-response curve for hepatotoxicity lies to the right of the lethal dose of a drug, so that hepatotoxicity is not seen. However, an episode of hepatic stress from an inflammatory response or other causes may shift the dose-response curve to the left to expose a hepatotoxic response in the range of therapeutic drug doses (B).

with the potential to cause these reactions in patients (Kaplowitz, 2005). This failure is due to our lack of understanding of the basis for these reactions. Although several hypotheses to explain them have emerged over the years, the reactions remain poorly understood. One possibility is that a stress occurring independently and sporadically during drug therapy renders a patient sensitive to liver injury. This hypothesis is depicted in Fig. 4B. In an unstressed individual, the liver may not appear as a target for toxicity for a drug because the doses needed to cause hepatotoxicity are very large. Indeed, the doses required might even be greater than the lethal dose, and therefore injury to liver would not be observed for such a drug because death occurs at doses that are smaller. To coin a corollary to Paracelsus' maxim, "all organs are susceptible to injury at some dose; thus, it is only death's intervention that separates a target from a nontarget organ" (Fig. 4B).

From an intrinsic hepatotoxicity perspective, a "good drug" is one that is pharmacologically efficacious and has a dose-response curve for hepatotoxicity that lies to the right of the lethal dose. However, an acute stress capable of increasing the sensitivity of the liver to injury from drug exposure would have the effect of shifting the dose-response curve for liver injury to the left. If this shift were pronounced enough, the liver would suddenly appear as a "target organ," and the resultant toxicity would demonstrate all of the characteristics of an idiosyncratic reaction. That is, the reaction would be unpredictable unless the stress itself was known and predictable. Moreover, the relationship of the liver injury to drug dose might be obscured by the shifting back and forth of the dose-response curve over time due to the sporadic occurrence of the causal stress. There might be other considerations as well; for example, a stress that reduces cytochrome P450-mediated metabolism can retard clearance of a drug and thereby enhance its plasma concentration, increasing the risk for toxicity (Morgan, 2009).

Such stresses are represented in some of the sensitivity factors listed in Table 2, among which is inflammation. As suggested above, inflammation can be viewed as a collage of stresses that can interact with drugs or other agents to produce liver injury. Inflammatory episodes are commonplace and are associated with numerous diseases, including arthritis, viral hepatitis, bacterial infections, periodontal disease, asthma, and many others. In addition, increases in translocation of LPS and other inflammagens from the intestine into the circulation can be prompted by alcohol consumption, alterations in diet, and other factors (reviewed in Ganey et al., 2004). Interaction of a drug with a sporadically occurring inflammatory episode could explain the unpredictable onset of idiosyncratic adverse drug reactions (IADRs) and their apparent lack of relationship to dose.

TABLE 2
Some determinants of individual sensitivity to hepatotoxicants

Age
Gender
Metabolism
Immunologic reactions
Reserve capacity
Absorption/distribution
Coexisting disease
Inflammation
Coexposures
Nutritional status

This drug-inflammation interaction hypothesis has been presented from the standpoint of an inflammatory stress enhancing the toxicity of a drug (Fig. 4B). However, it is equally plausible that a drug could enhance sensitivity of the liver to a potentially hepatotoxic inflammagen such as LPS. In this case, it may be the dose-response curve for the inflammagen that is shifted to the left by drug exposure, placing the curve into the range of concentrations of the inflammagen to which the patient is concomitantly exposed [Fig. 5(a)]. This could happen, for example, if the drug enhanced the sensitivity of hepatocytes to injury from inflammatory factors produced as a result of LPS exposure. Alternatively or in addition, the drug might enhance exposure to the inflammagen to the point at which hepatotoxic concentrations are attained [Fig. 5(b)]. A drug could enhance exposure to LPS, for example, by injuring the intestine to allow greater translocation of LPS into the circulation, thereby increasing LPS exposure into the range of hepatotoxic doses.

Animal Models of IADRs

Due to the rare occurrence of most IADRs and since patients are not typically evaluated until well after hepatotoxicity has developed, it has been difficult to mount incontrovertible evidence in humans for any hypothesis about the modes and mechanisms underlying these reactions. Likewise, most of the offending drugs are not hepatotoxic in the usual animal tests, so gaining insight from animal studies has been limited. Over the past few years, however, the inflammatory stress hypothesis has led to the emergence of animal models in which liver injury from IADR-associated drugs has been reproduced in rodents. Mostly, these models have involved cotreating rats or mice with a nontoxic dose of a drug and an inflammatory but nonhepatotoxic dose of LPS.

The use of trovafloxacin has been restricted because it has been associated with severe idiosyncratic hepatotoxicity in patients. Cotreatment of either rats or mice with nontoxic doses of trovafloxacin and LPS resulted in rapidly developing hepatotoxicity (Waring et al., 2006; Shaw et al., 2007). By contrast, levofloxacin, which does not share the IADR liability of trovafloxacin (De Sarro and De Sarro, 2001), did not synergize with LPS to cause liver injury in animals. Thus, the propensity of the two drugs to cause human IADRs

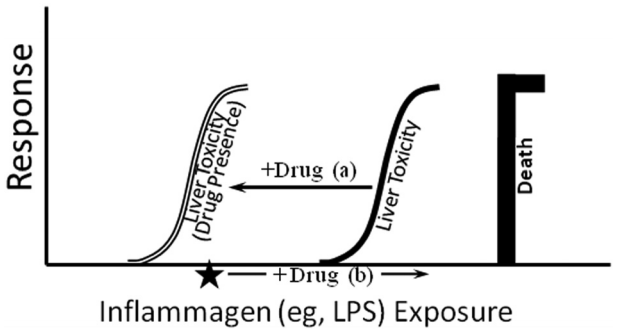

Fig. 5. Drugs may increase susceptibility to inflammatory liver injury. Humans and animals are typically exposed to inflammagens such as LPS at doses far below those that cause injury to liver or other tissues (star). Drugs can increase the risk of inflammatory liver injury by increasing the sensitivity of the liver to inflammatory injury (a) or by increasing exposure to an inflammagen (b). The latter can happen, for example, if the drug affects the intestine to increase the translocation of LPS or bacteria into the portal circulation.

matched their capacity to interact with LPS to cause liver injury in animals. Likewise, chlorpromazine and ranitidine have been associated with numerous reports of hepatotoxicity in humans, and both of these drugs interact with nontoxic doses of LPS, resulting in liver injury (Buchweitz et al., 2002; Luyendyk et al., 2003; Deng et al., 2009).

As noted above, diclofenac and sulindac are examples of NSAIDs that cause idiosyncratic hepatotoxicity (Lewis et al., 2002; Boelsterli, 2003; O'Connor et al., 2003). In rats, LPS converted a nontoxic dose of diclofenac into one that injured the liver (Deng et al., 2006). Recently, sulindac was found to interact similarly with LPS (Zou et al., 2009). These results are of particular interest because cyclooxygenase inhibitors cause intestinal injury in both humans and rodents (Seitz and Boelsterli, 1998; Atchison et al., 2000; O'Connor et al., 2003), and such injury can increase movement of LPS or bacteria from the intestine into the circulation. Indeed, large doses of diclofenac by themselves are hepatotoxic to rodents, and the liver injury is associated with accumulation of bacteria in liver and can be eliminated by pharmacologic sterilization of the intestinal tract (Deng et al., 2006). This suggests that translocated LPS or bacteria contribute to diclofenac hepatotoxicity. In contrast, the hepatotoxic interaction between LPS and a smaller, nontoxic dose of diclofenac was not diminished by intestinal sterilization; this suggests that the drug does not act solely by increasing LPS exposure and that it may also enhance hepatocellular sensitivity to LPS-induced inflammatory stress (Deng et al., 2006).

Much remains unknown about the nature of the interaction between IADR-producing drugs and inflammatory stress. Histopathologically, the lesions in LPS/drug-treated animals for all of the IADR-associated drugs mentioned above comprised predominantly midzonal hepatocellular necrosis accompanied by neutrophilic infiltrate. Factors that initiate the lesions are unknown; however, cytokines, neutrophils, and an activated hemostatic system seem to be commonly involved in the progression of injury. This could suggest that the drugs act by enhancing sensitivity of the liver to LPS (Fig. 5), because the appearance of the lesions and the known progression factors are similar to those that characterize liver injury from large, hepatotoxic doses of LPS. However, some qualitative differences in response between the drug-LPS interaction models and LPS hepatotoxicity exist, so the picture is not yet entirely clear. Regardless, it is of interest that at least some of the progression factors involved in LPS interaction with IADR-producing drugs are the same as those involved with LPS interaction with intrinsic hepatotoxicants (see Ganey et al., 2004).

As is true for other IADR theories, supporting evidence in humans for inflammation-drug interaction as a cause of IADRs is currently sparse. For both chlorpromazine and ranitidine, over half of the published case reports mention prodromal signs in patients (fever, vomiting, diarrhea, etc.) that are consistent with a predisposing inflammatory episode. It might not be merely coincidental that the two classes of drugs with the greatest liability for causing idiosyncratic drug-induced liver injury are antibiotics and NSAIDs, because such drugs are used to treat conditions associated with inflammation. Bacteria dying from antibiotics can release cellular components such as LPS that are inflammatory. People who consume NSAIDs typically have inflammatory conditions such as arthritis, and polymorphisms that lead to impaired production of anti-inflammatory interleukin 10 and interleukin 4 have been reported in patients who suffered diclofenac hepatotoxicity (Aithal et al., 2004). Polymorphisms such as these could enhance the sensitivity of patients to inflammatory mediators released in response to LPS translocated from an intestine irritated by the NSAID. However, convincing evidence in humans will require additional study.

Summary and Perspective

Susceptibility factors seem to be important in idiosyncratic as well as intrinsic hepatotoxicities. Indeed, the most basic of toxicologic principles points to the possibility that some idiosyncratic reactions differ from intrinsic ones only in the position of the dose-response curve for hepatotoxicity relative to those for death and pharmacologic effect. That is, the liver can be easily recognized as a target organ for intrinsic hepatotoxicants because the dose-response curve for toxicity lies clearly to the left of the lethal dose and usually not too far rightward from the curve for pharmacological effect (e.g., as with APAP). For at least some agents that cause idiosyncratic reactions, the only difference from intrinsic hepatotoxicity may be that the dose-response curve for hepatotoxicity lies to the right of the lethal dose. In both cases, inflammatory or other stresses are capable of causing a leftward shift in the dose-response relationship for hepatotoxicity. Whether the toxicity appears to be "intrinsic" or "idiosyncratic," the result can be the same: if the curve for hepatotoxicity shifts enough to the left so that it reaches into the range of doses used pharmacologically, a hepatotoxic reaction would be expected to occur at or near doses used for drug therapy. Thus, the ending to this tale is that, like Dr. Jekyll and Mr. Hyde, the two villains appear to be different but seen in the proper light, they might be recognized as one in the same. If there is to be a sequel with a happy ending, it will emerge from the understanding of determinants of sensitivity and using them to develop predictive in vivo and in vitro models that will improve drug safety.

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Address correspondence to: Dr. Robert A. Roth, Department of Pharmacology and Toxicology, Center for Integrative Toxicology, 221 Food Safety and Toxicology Bldg., Michigan State University, East Lansing, MI 48824. E-mail: rothr@msu.edu